

Biochemical assessment of patients following ketogenic diets for epilepsy: current practice  
in the UK and Ireland

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## Summary

*Objective:* Biochemical assessment is recommended for patients prior to initiating and following a ketogenic diet (KD). There is no published literature regarding current practice in the UK and Ireland. We aimed to explore practice in comparison to international guidelines, determine approximate costs of biochemical testing in KD patients across the UK and Ireland, and promote greater consistency in KD services nationally.

*Methods:* A survey was designed to determine the biochemical tests requested for patients at baseline, 3-, 6-, 12-, 18- and 24-months+ on KD. The survey was circulated to 39 centres across the UK and Ireland.

*Results:* 16 centres completed the survey. Full blood count, electrolytes, calcium, liver function tests (LFTs), lipid profile and vitamin D were requested at all centres at baseline, in keeping with international guidelines. Bicarbonate, total protein and urinalysis were less consistently requested. Magnesium and zinc were requested by all centres, despite not being specifically recommended for pre-diet evaluation in guidelines.

Urea and electrolyte profiles and some LFTs were consistently requested at follow-up, in accordance with guidelines. Other LFTs and renal tests, full blood count, lipid profile, acylcarnitine profile, selenium, vitamin D and urinalysis were less consistently requested at follow-up.

The mean costs of the lowest and highest number of tests requested at baseline in our participating centres was £167.54 and £501.93; the mean costs of the lowest and highest number of tests requested at 3-month follow-up was £19.17 and £450.06.

*Significance:* Biochemical monitoring of KD patients varies widely across the UK and Ireland and does not fully correspond to international best practice guidelines. With an ongoing

drive for cost-effectiveness within healthcare, further work is needed to streamline practice whilst ensuring patient safety.

Key words: high-fat, low-carbohydrate, laboratory

Key points

- Baseline tests are mostly in keeping with international guidelines, except for the addition of magnesium and zinc
- Not all tests were not consistently requested by all centres at follow-up, despite recommendations
- Mean costs of baseline tests ranged from £167.54-£501.93
- Mean costs of 3-month follow-up tests ranged from £19.17-£450.06

## Introduction

Ketogenic diets (KDs) are high-fat, low-carbohydrate, moderate protein diets used as a treatment option for drug-resistant epilepsy. KDs are the treatment of choice for neurometabolic disorders such as glucose transport type 1 deficiency syndrome<sup>1</sup> and pyruvate dehydrogenase deficiency<sup>2</sup>, and are effective in reducing seizure frequency in approximately one third of patients with epilepsy<sup>3</sup>.

KDs are inappropriate for some individuals, for example, with primary carnitine deficiencies and  $\beta$ -oxidation defects and thus screening biochemical tests to rule out such disorders are a crucial part of pre-diet assessment. KDs cause the body's metabolism to adjust, utilising ketone bodies rather than glucose as its primary energy source. Due to stringent dietary restriction, individuals following a KD are often at risk of vitamin and mineral deficiencies<sup>4,5</sup> and therefore close biochemical monitoring is required to ensure nutritional adequacy and safety.

International consensus guidelines regarding optimal care of paediatric patients on KD therapies have been recently updated, including which biochemical tests (blood and urine) should be completed prior to diet initiation and during the treatment period<sup>6</sup>. These follow on from KD care guidelines for resource-limited countries published in 2015, including required and desired biochemical monitoring<sup>7</sup>.

Over the past two decades, the number of KD services in the UK and Ireland has increased from 22 to 39, with a concomitant surge in the number of patients on diet (from 101 in 2000<sup>8</sup> to 754 in 2017<sup>9</sup>). Centres in the UK and Ireland have local guidance for biochemical assessment and monitoring for KD patients but, to date, there has been no comparison nor consolidation of existing practices. Many of the biochemical tests required during KD

treatment must be sent to specialist centres, further inflating costs and delays to treatment, conflicting with the current climate of the National Health Service (NHS), where services aim to be clinically and cost-effective. The 2018 international recommendations involved a high proportion of non-UK healthcare professionals from countries where costs are paid by insurance or by the patient privately, which could lead to disparities in practice.

We aimed to i) explore current practice of biochemical testing in KD patients across the UK and Ireland in comparison to international guidelines, ii) determine approximate costs of biochemical testing in KD patients across the UK and Ireland, and iii) promote greater consistency in KD services nationally. To our knowledge, this is the first investigation of its kind. It is hoped that this work will help determine adherence to guidelines with regards biochemical monitoring of patients with epilepsy following a KD in the UK and Ireland, and whether action needs to be taken to streamline practice whilst ensuring patient safety and financial benefit.

## Methods

A survey was designed by the Ketogenic Dietitians Research Network (KDRN) (a consortium of KD Healthcare Professionals) to identify biochemical tests requested in patients commencing and following a KD for epilepsy and metabolic disorders in centres in the UK and Ireland. The ketogenic dietitians at each centre were asked to list all biochemical investigations requested at baseline (pre-diet), 3-, 6-, 12-, 18- and 24-months post diet initiation during routine follow up (and other time points if applicable), as well as the frequency of biochemical follow-up for patients on diet longer than two years (the point at which, routinely, patients and medical teams may consider discontinuing the diet). Centres

were also invited to share the cost of each biochemical test requested as part of their KD service, if available, which provided an indication of the financial range anticipated for tests at both baseline and review.

The survey was disseminated via email to 39 services in the UK and Ireland. Following the initial email, two follow-up emails were sent in an attempt to obtain more responses. All answers were pseudo-anonymised and results were compared to the laboratory assessments recommended in international best practice guidelines<sup>6</sup>, as outlined in Table 1.

## Results

16 centres completed the survey: 15 paediatric centres (of which 14 were NHS) and one non-NHS joint adult and paediatric centre.

The number of patients referred annually for KD treatment in each of these centres, the patient population (paediatrics or adults), and the type of centre (primary, secondary or tertiary care) are outlined in Table 2.

### *Current practice and comparison to international guidelines*

A total of 63 different biochemical tests were requested across the participating centres.

Table 3 outlines recommended tests, clustered into clinical groups, and lists which groups of tests were requested by all, by 90-99%, by 75-90%, by 50-75% and then by <50% of participating centres. A list of all tests (ungrouped) and the percentage of centres that requested each test at each time point can be found in the Supplementary Table.

### *Baseline monitoring*

Full blood count, electrolytes, calcium, liver function tests (LFTs), lipid profile and vitamin D were requested at all centres at baseline, in keeping with international guidelines (Table 3).

Bicarbonate, total protein and urinalysis are recommended in international guidelines but were not consistently requested by our participating centres. Magnesium and zinc were also requested by all centres, despite not being specifically mentioned for pre-diet evaluation in international guidelines.

#### *Follow-up monitoring*

Twelve centres requested biochemical tests routinely at 3-, 6-, 12-, 18- and 24-months post-diet initiation; two centres did not request any tests at 3 months, one centre that did not request any tests at 18 months, and one centre requested tests at 3-months and then 6-monthly thereafter (testing requested at 3-, 9-, 15-months post-diet initiation).

Urea, creatinine and electrolytes, alanine aminotransferase (ALT) and alkaline phosphatase (ALP) were requested by all centres at 3-, 6-, 12-, 18- and 24-month follow-up (centres that routinely requested biochemical tests at these respective time points). Full blood count, lipid profile and albumin were requested by each of our centres at every review except for the 18-month point. Other components of renal profile and liver function tests, acylcarnitine profile, selenium, vitamin D and urinalysis were less consistently requested at follow-up (Table 3).

13/16 (81%) centres requested non-fasting lipid profiles, both at baseline and review, despite recommendations for a fasting lipid profile. Seven of these 13 requested non-fasting lipid profiles, but would repeat in a fasted state if initial results were abnormal.

#### *Long-term follow-up*

For those centres following patients up for more than 2 years: 10/16 (63%) centres requested 6-monthly monitoring for patients following a KD, in keeping with guidelines

advising six-monthly visits after following a KD for 1 year. 5/16 (33%) centres requested yearly monitoring and 1/16 (6%) had no protocol.

### *Cost implications*

The mean costs of the lowest and highest number of tests requested at baseline in our participating centres was £167.54 and £501.93; the mean costs of the lowest and highest number of tests requested at 3-month follow-up was £19.17 and £450.06. For comparison, the mean cost per visit of all biochemical tests recommended in international guidelines was £108.96 at baseline and £126.09 at review. The minimum, maximum and mean cost per test can be found in Table 4.

### Discussion

Our study illustrates that biochemical assessment and monitoring of KD patients with epilepsy vary widely across the UK and Ireland and do not fully correspond to international best practice guidelines<sup>6</sup>. This variability is reflected in the associated costs of biochemistry testing. To our knowledge, there are no other previously published works outlining which biochemical tests are requested in KD patients in the UK and Ireland and their financial impact.

Variability of practice is inevitable, due to differing patient populations in each centre and the acute needs of individuals, particularly in the complex cohort that commence dietary therapy for refractory epilepsy. However, the level of variability amongst our participating centres seems striking. This may be partially explained by the fact that the expansion of KD



services in the UK and Ireland is a recent and somewhat sporadic phenomenon<sup>9,10</sup>. Only in recent years have technological advances and the creation of national groups, such as KDRN, facilitated liaison across participatory centres, promoting communication and sharing of resources. Research study protocols, such as those from the original randomised controlled trial at Great Ormond Street<sup>11</sup> and Ketogenic Diet in Infants with Epilepsy (KIWE)<sup>12</sup> may also influence what tests are requested at participating centres.

Our costing results, although approximate, indicate that biochemical testing for KD patients can have a substantial financial impact on services, as well as highlighting the variability between centres. The final cost to an individual centre will vary, as large teaching hospitals can often benefit from lower costings due to higher workload and are more likely to have specialist tests available on site. Between hospital laboratories, the items included in a profile vary. In addition, the type of technology used (for example, high throughput minimal intervention automated analysers versus mass spectrometry for 25-hydroxy vitamin D3) and, in some cases, the interpretation of the laboratory price list can also impact the final cost: some centres may ask for the cost to measure a set of electrolytes, liver function tests and a bone profile, whereas asking for a 'full profile' should cost slightly less due to the overlap in tests. Notwithstanding these caveats, a difference of £334.39 between minimum and maximum requested baseline tests and £430.89 for 3-month review tests in our participating centres is noteworthy.

Any 'lesser' costs in KD laboratory monitoring need to be balanced against the possible increased risk of complications, with associated costs. Even the cost of 'complete' KD monitoring may be less than treatment with a new antiepileptic drug, which can cost up to approximately £100/month<sup>13</sup>, as well as the costs implicated in seizure-related

complications. On the other hand, it may not be appropriate to test for each recommended parameter at every review, such as vitamin D, due to the time taken for changes to take effect<sup>14,15</sup>.

Magnesium and zinc were requested by all our participating centres at baseline, despite not being included in international best practice guidelines for pre-diet evaluation. This may represent a cost saving *if* unnecessary in most patients. No report of zinc deficiencies in individuals following a KD have been identified, although classical KDs with a 2:1 ratio or higher fail to meet the dietary reference intake for zinc, despite 'selection of nutrient dense foods'<sup>16</sup>. One may argue that if mentioned as 'optional' to measure at review, as in international guidelines, baseline assessment of zinc would also be appropriate. Mean plasma magnesium levels have been found to decrease in children on the classical KD<sup>4</sup> and the diet has been shown to provide suboptimal magnesium levels<sup>16</sup>. Intakes of zinc and magnesium may be suboptimal even prior to KD initiation: 3-27% and 0-50% of the UK population surveyed in the latest National Diet and Nutrition Survey (including males and females across all age groups above 1.5years) do not meet the lower reference nutrient intake (RNI) for zinc and magnesium respectively<sup>17</sup>.

The discrepancies between which tests were requested at all review appointments in our centres compared to international recommendations may be predominantly cost-driven, particularly considering that the 2018 guidelines involved a high proportion of non-UK healthcare professionals from countries where costs are paid by insurance or by the patient privately, compared to the government-funded UK National Health Service, which could potentially be considered 'resource-limited'. Furthermore, whilst NICE recommends KDs for paediatric refractory epilepsy<sup>18</sup>, it does not suggest recommendations for monitoring and so

there is no UK cost-effective reference guidelines. In previous guidelines issued for resource-limited regions, bicarbonate was deemed mandatory at baseline and review, and urinalysis and lipid profile were mandatory at review<sup>7</sup>.

Published reports of abnormalities in individuals following KDs may provide guidance as to whether it is necessary to request the 'missing' parameters at each review in UK and Ireland centres. Besides dyslipidaemia, which is one of the most well-cited (although often transient) biochemical side effects of KDs, occurring in approximately 12% of children studied prospectively on a KD<sup>19</sup>, reports of abnormalities of other parameters are uncommon. Individuals following a KD have been shown to have reduced serum 25-hydroxyvitamin D concentration (as were individuals solely on antiepileptic drugs) and reduced bone mass (to a greater extent than in individuals solely on drug therapy)<sup>20</sup>; another study found 25-hydroxyvitamin D levels (which were mostly low at diet initiation) to improve initially on commencement of a KD, including supplementation, but to decline after three months<sup>21</sup>. Selenium deficiency has been reported in 66 individuals on KD treatment<sup>22-25</sup>, associated with cardiomyopathy in two of these patients<sup>23,25</sup> and sudden cardiac death in another two<sup>24</sup>. A trend of decreasing plasma selenium was noted in participants of the original randomised controlled trial at GOSH, with a significant decrease between baseline and six months in children on the classical KD, although mean plasma selenium was maintained within the GOSH reference ranges<sup>4</sup>.

In view of the possible association of selenium with cardiac abnormalities, monitoring of selenium seems significant, although prolonged QT interval has also been reported in three cases following a KD in the absence of selenium deficiency<sup>26</sup>. The frequency of testing at review, particularly in the 12-24-month follow-up period, may need revisiting specifically for

the UK and Ireland in order to balance clinical safety with the potential financial/logistical constraints of 6-monthly testing.

This study has several limitations. Only 16 of the 39 centres that (to our knowledge) practice KDs within the UK and Ireland volunteered to answer the survey; practice in the other centres remains unknown. The survey was not validated and could be subject to reporter error. Our cost estimations would also improve in accuracy with greater centre participation. A follow-up study to assess whether rate of complications is correlated with frequency and 'completeness' of laboratory monitoring would be pertinent.

Biochemical monitoring of KD patients varies widely across the UK and Ireland and does not fully correspond to international best practice guidelines. With an ongoing drive for cost-effectiveness within the NHS, further work is needed to streamline practice whilst ensuring patient safety, both for financial benefit without clinical compromise for patients, perhaps with the creation of nationwide-specific guidelines. Further research into biochemical monitoring of KDs worldwide would be of interest to compare to practice in the UK and Ireland.

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#### Disclosure of Conflicts of Interest

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We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

## References

- 1 Klepper J, Leiendecker B. GLUT1 deficiency syndrome--2007 update. *Dev Med Child Neurol* 2007; 49: 707-716.
- 2 Wexler ID, Hemalatha SG, McConnell J, et al. Outcome of pyruvate dehydrogenase deficiency treated with ketogenic diets. Studies in patients with identical mutations. *Neurology* 1997; 49: 1655-1661.
- 3 Martin-McGill KJ, Jackson CF, Bresnahan R, et al. Ketogenic diets for drug-resistant epilepsy. *Cochrane Database Syst Rev* 2018; 11: CD001903.
- 4 Christodoulides SS, Neal EG, Fitzsimmons G, et al. The effect of the classical and medium chain triglyceride ketogenic diet on vitamin and mineral levels. *J Hum Nutr Diet* 2012; 25: 16-26.
- 5 Zupec-Kania B. Micronutrient content of an optimally selected ketogenic diet. *Journal of the American Dietetic Association* 2003; 103: 8-9.
- 6 Kossoff EH, Zupec-Kania BA, Auvin S, et al. Optimal clinical management of children receiving dietary therapies for epilepsy: Updated recommendations of the International Ketogenic Diet Study Group. *Epilepsia Open* 2018; 3: 175-192.
- 7 Kossoff EH, Al-Macki N, Cervenka MC, et al. What are the minimum requirements for ketogenic diet services in resource-limited regions? Recommendations from the International League Against Epilepsy Task Force for Dietary Therapy. *Epilepsia* 2015; 56: 1337-1342.
- 8 Magrath G, MacDonald A, Whitehouse W. Dietary practices and use of the ketogenic diet in the UK. *Seizure* 2000; 9: 128-130.
- 9 Whiteley VJ, Martin-McGill KJ, Carroll JH, et al. Nice to know: impact of NICE guidelines on ketogenic diet services nationwide. *J Hum Nutr Diet* 2019;
- 10 Whiteley V, Martin K, Carroll J, et al. NICE to know: Impact of NICE Guidelines on Ketogenic Diet Services Nationwide. *Dev Med Child Neurol* 2018; 59: 84.
- 11 Neal EG, Chaffe H, Schwartz RH, et al. The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial. *Lancet Neurol* 2008; 7: 500-506.
- 12 Titre-Johnson S, Schoeler N, Eltze C, et al. Ketogenic diet in the treatment of epilepsy in children under the age of 2 years: study protocol for a randomised controlled trial. *Trials* 2017; 18: 195.
- 16 Zupec-Kania B, Zupanc ML. Long-term management of the ketogenic diet: seizure monitoring, nutrition, and supplementation. *Epilepsia* 2008; 49 Suppl 8: 23-26.
- 19 Cai QY, Zhou ZJ, Luo R, et al. Safety and tolerability of the ketogenic diet used for the treatment of refractory childhood epilepsy: a systematic review of published prospective studies. *World J Pediatr* 2017; 13: 528-536.
- 20 Hahn TJ, Halstead LR, DeVivo DC. Disordered mineral metabolism produced by ketogenic diet therapy. *Calcif Tissue Int* 1979; 28: 17-22.
- 21 Bergqvist AG, Schall JI, Stallings VA. Vitamin D status in children with intractable epilepsy, and impact of the ketogenic diet. *Epilepsia* 2007; 48: 66-71.
- 22 Arslan N, Kose E, Guzel O. The Effect of Ketogenic Diet on Serum Selenium Levels in Patients with Intractable Epilepsy. *Biol Trace Elem Res* 2017; 178: 1-6.
- 23 Bergqvist AG, Chee CM, Lutchka L, et al. Selenium deficiency associated with cardiomyopathy: a complication of the ketogenic diet. *Epilepsia* 2003; 44: 618-620.
- 24 Bank IM, Shemie SD, Rosenblatt B, et al. Sudden cardiac death in association with the ketogenic diet. *Pediatr Neurol* 2008; 39: 429-431.
- 25 Sirikonda NS, Patten WD, Phillips JR, et al. Ketogenic diet: rapid onset of selenium deficiency-induced cardiac decompensation. *Pediatr Cardiol* 2012; 33: 834-838.
- 26 Best TH, Franz DN, Gilbert DL, et al. Cardiac complications in pediatric patients on the ketogenic diet. *Neurology* 2000; 54: 2328-2330.